## REMARKS

The presently claimed invention concerns a specific compound and the use of the compound in the treatment of hepatocellular carcinoma.

Applicants have canceled claims 1-62 and added new claims 63-65. Support for the new claims is found, for example, in the original claims. No new matter has been added.

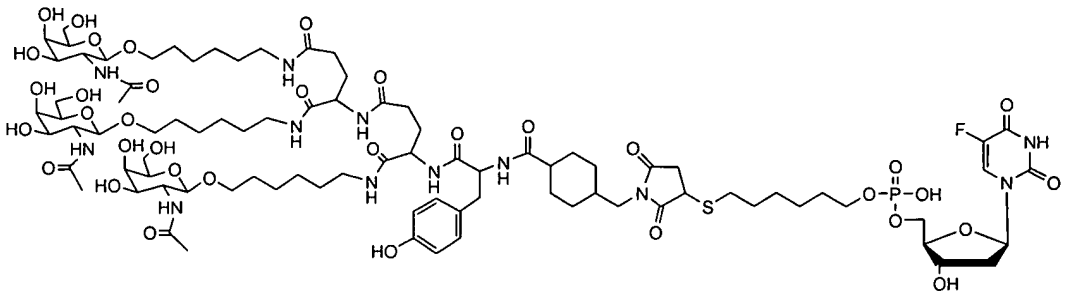
Applicants appreciate the withdrawal of the previous restriction requirement.

### Double Patenting

The Examiner rejected previously pending claims 1 and 31 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 14 of U.S. Patent No. 5,994,517 to Ts'o et al. ("the '517 patent"). Claims 1 and 31 of the present application have been cancelled. It is believed that the currently pending claims are patentably distinct from the claims of the '517 patent, and Applicants respectfully request that this rejection be withdrawn.

### Rejections Under 35 U.S.C. §102(b)

The Examiner rejected previously pending claims 1, 2, 11, 16, 19, 20-31, 32 and 42-54 under 35 U.S.C. §102(b) as anticipated by the '517 patent. Claims 1-62 have been canceled. Present claim 63 is drawn to a specific compound, referred to as "YEE(ahGalNAc)$_3$-SMCC-poFU" and "po 1-mer" in the present application. Claim 64 is drawn to the use of this compound in the treatment of hepatocellular carcinoma. Claim 65 is drawn to a pharmaceutical composition that contains the compound of claim 63. The claimed compound, depicted below, is a conjugate that includes: a glycosylated peptide which recognizes the asialoglycoprotein receptor, a non-peptide linker, and a single molecule of 5FdU.



glycosylated peptide non-peptide linker 5FdU

Clearly, the '517 patent does not disclose the presently claimed molecule. Thus, the '517 patent cannot anticipate any of the present claims. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

Rejections Under 35 U.S.C. §103

The Examiner rejected previously pending claims 1-62 under 35 U.S.C. §103(a) as obvious in view of the '517 patent taken with Wu et al. (*Proc. Nat'l Acad Sci* 80:3078, 1983). According to the Examiner, the '517 patent teaches a conjugate having: a glycosylated peptide that binds a hepatic receptor; a bifunctional linker; and a "monomer or polymer comprising at least one nucleotide or analog of that inhibits nucleotide synthesis in a sequence independent manner". Also according to the Examiner, Wu et al. teaches that conjugates containing a hepatic ligand can be used to target a hepatic receptor for the delivery of a chemotherapeutic agent. Based on these assertions, the Examiner concludes that it would have been obvious to combine the teachings of the '517 patent and Wu et al. in order to create a conjugate that includes: a glycosylated peptide that binds to a hepatic receptor; a bifunctional linker; and "a monomer or polymer comprising at least one nucleotide or analog thereof that inhibits nucleic acid synthesis in a sequence independent manner for the inhibition of . . . hepatocarcinoma".

Applicants disagree with the Examiner's characterization of the cited prior art and the Examiner's conclusion regarding obviousness. First, the cited references do not contain all of the elements of the presently claimed invention. Moreover, even if the cited references

contained all of the elements of the presently claimed invention, which they do not, the cited references neither provide any reason to combine the elements to arrive at the presently claimed invention nor do they provide one with a reasonable likelihood of success if one were to arrive at the presently claimed invention. As the Court of Appeals for the Federal Circuit has explained,

> A proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

*In re Vaeck* , 947 F.2d 488, 493 (Fed. Cir. 1991).

When the two factors discussed by the court in *In re Vaeck* are properly analyzed it becomes clear that the cited prior art does not render the presently claimed invention obvious. Indeed, the cited prior art actually teaches away form the presently claimed invention, further supporting Applicants' position that the presently claimed invention is not obvious in view of the cited prior art.

The cited prior art does not suggest making the claimed compound or carrying out the claimed methods

As noted above, the present claims are drawn to a specific molecule, depicted above. While it is true that the '517 patent discloses a number of conjugates that include the glycosylated peptide and non-peptide linker portions of the presently claimed molecule, neither the '517 patent nor Wu et al. discloses 5FdU. Moreover, neither reference suggests linking 5FdU to a ligand for the asialoglycoprotein receptor. The Examiner acknowledges that the '517 patent does not disclose 5FdU and does not suggest that Wu et al. does disclose 5FdU. However the Examiner argues that the '517 patent "teaches that the conjugates may comprise oligodeoxynucleotides containing all 2'-O-modified nucleosides and deoxynucleosides ... which encompass 5FdU and various sugar modifications."

The teachings of the '517 patent noted by the Examiner do not amount to a teaching of 5FdU for at least two independent reasons. First, there are large numbers of 2'-O-modified nucleosides and deoxynucleosides. The disclosure of this broad class of compounds does not amount to a disclosure of 5FdU. Second, the '517 patent does not disclose or suggest the use of single nucleotides of any type. Instead, the '517 patent repeatedly states that the conjugates are to be used for the delivery of oliognucleotides to hepatic cells. For example, the '517 patent states that it is "an object of the invention to provide homogeneous oligodeoxnucleoside methylphosphonate conjugates, which contain non-biodegradable methylphophonate internucleotide linkages". Col. 2, lines 55-58. There does not appear to be any teaching or suggestion to create a conjugate having a single nucleotide. As discussed in greater detail below, Wu et al. does not teach the use of a nucleotide of any type. Thus, the cited references completely lack any teaching regarding 5FdU.

There is no explicit or implicit teaching in the cited prior art references to modify the conjugates of the '517 patent by substituting the oligonucleotide portion of the conjugates of the '517 patent with a single nucleotide of any type. Indeed, the entire thrust and purpose of the teachings of the '517 patent is just the opposite. Instead of teaching conjugation of an asialoglycoprotein receptor ligand to a single nucleotide, the patent teaches the conjugation of such a ligand to an oligonucleotide that cannot be degraded to single nucleotides. For example, the '517 patent explains that it is "an object of the invention to provide homogenous oligodeoxynucleotide methylphophate conjugates, which contain non-biodegradable methylphophonate internucleotide linkages" (col. 2, lines 55-58). Thus, not only does the '517 patent disclose only the use of oligonucleotides, particular care is taken to specify that the oligonucleotides are of the type that resist degradation to single nucleotides. Contrary to the Examiner's assertion, the '517 patent simply does not disclose a conjugate that includes nucleotide "monomer"

The cited references also do not suggest the use of an agent that can "inhibit nucleic acid synthesis in a sequence independent manner" as stated by the Examiner. Turning first to the '517 patent, a careful review of the specification does not reveal any teaching or suggestion to

use agent of any type that inhibits nucleic synthesis in a sequence independent manner as quoted by the Examiner. In contrast, the oligonucleotides of the '517 patent are "gene specific" in that they have "a sequence that is complementary to a portion of a gene or a portion of a mRNA molecule found in the tissue or cell type targeted by the conjugate." Col. 4, lines 6-11. Thus, the action of the conjugates described in the '517 patent is intended to be sequence dependent, not sequence independent. Thus, far from teaching a sequence independent inhibitor of nucleotide synthesis, the '517 patent teaches exactly the opposite.

Wu et al. does not provide what the '517 patent lacks. Wu et al. does not teach the use of any type of inhibitor of nucleic acid synthesis, much less a sequence independent inhibitor of nucleic acid synthesis.

Even if the cited references did teach or suggest either 5FdU or some other nucleotide that is a sequence independent inhibitor of nucleic acid synthesis, they still could not render the present claims obvious. This is because there is no explicit or implicit suggestion in the references to modify the conjugates described '517 patent to replace the oligonucleotide portion of the conjugate with an agent that inhibits nucleic acid synthesis in a sequence independent manner, much less 5FdU. In an effort to identify the motivation to alter the conjugates of the '517 patent, the Examiner argues that the '517 patent teaches that it can be useful to target drugs to hepatic cells and that Wu et al "bridges the nexus for abnormal cellular proliferation or hepatocarcinoma as it teaches that conjugates containing the claimed hepatic ligands can be used to target hepatic receptors for the delivery of chemotherapeutic agents". The Examiner's argument is misguided. Wu et al. does not teach the use of hepatic receptors to target delivery of chemotherapeutic agents. Instead, Wu et al. teaches a conjugate that includes desialylated bovine fetuin linked to folonic acid, a methotrexate antagonist. This conjugate, which is predicted by Wu et al. to bind to the asialoglycoprotein receptor, is designed to deliver an antagonist of a cellular toxin, not a chemotherapeutic agent, to hepatic cells. Thus, Wu et al., far from suggesting targeting a chemotherapeutic agent to hepatocarcinoma cells to inhibit or kill the cells, suggests just the opposite: targeting an anti-chemotherapeutic agent to non-cancerous cells to rescue them from the deleterious effects of a separately administered chemotherapeutic agent.

Thus, the cited reference cannot be seen as suggesting, either implicitly or explicitly, making the claimed compound.

The cited prior art does not provide a reasonable expectation of success

Even if the cited references taught all of the elements of the presently claimed invention, which they do not, and even if the cited references provided a motivation to modify the conjugates of the '517 patent to create the presently claimed compound, which they do not, the cited references would still fail to render the present claims obvious. This is because the cited referenced do not provide one of ordinary skill in the art with a reasonable expectation of success. Indeed, Wu et al. suggests that one could not create a molecule that would effectively target an inhibitor of nucleic acid synthesis or any other chemotherapeutic agent to hepatocarcinoma cells. As Wu et al. explains,

> Whereas other investigators have shown that toxins can be delivered to differentiated cells, the results presented here demonstrate specific rescue of differentiated cells by a biochemical agent based on the presence of receptor-mediated endocytosis. Specific delivery of cytotoxins to malignant cells has been limited by the inherent difficulty presented by the disappearance of cellular functions in the undifferentiated state, thus making specific rescue of differentiated cells a reasonable alternative approach.

Wu et al. clearly suggests that a chemotherpeutic agent targeted to a hepatocarcinoma cell would not be effective. Thus, Wu et al. does not provide the reasonable expectation of success that must be present for a finding of *prima facie* obviousness.

The cited prior art teaches away from the claimed compounds and methods

Because Wu et al. suggests that it would be difficult to deliver a chemotherapeutic agent to a malignant cell via a receptor such as the asialoglycoprotein receptor, this reference actually teaches away from the claimed compound and methods and suggests instead a strategy of protecting non-cancerous cells. "A reference may be said to teach away when a person of

ordinary skill, upon reading the reference, ... would be led in direction divergent from the path that was taken by the applicants." *In re Gurley* 27 F.3d 551, 553 (Fed. Cir. 1984).

Applicants have shown that the claimed molecule actually is effective in reducing the size of hepatic tumors in mice. For example, as described in detail on pages 43-47 of the present application, the claimed molecule, referred to as po 1-mer in the specification, was administered to mice harboring a human hepatoma xenograft. Briefly, nude mice were injected subcutaneously with $10^8$ HepG2 cells. When the hepatic tumors reached 100 mg, treatment was initiated with po 1-mer using a variety of dosing regimes. Tumor growth was judged by direct measurement of the tumors. Treatment with po 1-mer at 10 mg/kg weekly resulted in reduced tumor size compared to no treatment controls, reduced mitotic index, and increased tumor necrosis. More pronounced results were observed when po 1–mer was administered at higher doses. Moreover, when po 1-mer was administered at 10 mg/kg twice weekly, tumors were not detectable after 6 weeks. As the Court of Appeals for the Federal Circuit has explained, that "the inventor achieved the claimed invention by doing what those skilled in the art suggested should not be done [is] a fact strongly probative of nonobviousness." *Kloster Speedsteel AB v. Crucible Inc.* 793 F.2d 1565, 1575 (Fed Cir. 1986).

In view of the forgoing, Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

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Respectfully submitted,

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